IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Bennett, C. Frank
App. No	:	10/559401
Filed	:	September 11, 2008
For	:	OLIGONUCLEOTIDE MODULATION OF CELL ADHESION
Examiner	:	Zara, Jane J.
Art Unit	:	1635
Conf No.	:	5614

PRE-APPEAL BRIEF CONFERENCE REQUEST

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

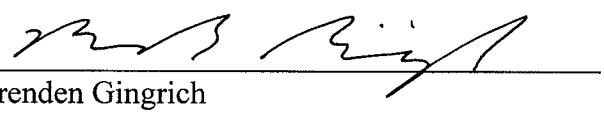
Dear Sir:

Appellants request review of the final rejection of claims 24, 26-30, 33-42, 44 and 45 under 35 U.S.C. § 103(a) in the Office Action dated May 2, 2011. The accompanying discussion of reasons Appellants believe the Examiner's rejection is in error is limited to five pages as required.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: October 26, 2011

By: 

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There are Clear Errors in the Examiner's Rejection under 35 U.S.C. § 103(a)

The Examiner has Failed to Establish a Prima Facie Case of Obviousness

All pending claims are rejected under 35 U.S.C. § 103(a) as obvious over Bennett et al. (WO 92/03139), Bennett et al. (US 6,077,833) and Pietrzkowski et al. (US 5,849,903), the combination in view of Wright et al. (US 5,795,876), Cook et al. (US 6,440,943) and Wolyniec et al. (*Am. J. Resp. Cell & Molec. Biol.*, 18:777-785 (1998)), the combination further in view of Wang et al. (US 6,403,566). *See Office Action* at page 2-3.

To establish a *prima facie* case of obviousness, the Examiner must establish that there is a reasonable expectation of success in practicing the claimed invention. Here, there must be a reasonable expectation of successfully administering the claimed compounds via the lung such that ICAM-1 expression is inhibited and eosinophil recruitment into the lung is reduced. For the reasons below, Appellants submit that the Examiner has not established a *prima facie* case of obviousness.

The Examiner's rejection depends on three assertions which are not supported by the evidence of record. The first is the assertion that Pietrzkowski teaches that "delivery [of] antisense to the lungs was routine in the art..." *Id.* at page 5. The second is that the references provide a reasonable expectation that administration of ICAM-1 antisense into the lungs "would provide for inhibition of ICAM1 expression" and the third assertion is that "would provide for the treatment effects claimed..." *Id.* at page 6. Appellants respectfully disagree.

Pietrzkowski does not establish that it is routine to administer antisense into the lung

The only express disclosure in Pietrzkowski of administering antisense directly into the lungs is a single sentence in a laundry list of administration routes which states:

> Still further, the oligonucleotides of the present invention can be administered ... as an aerosol directly to the lung, using for example ICN Biomedicals product no. SPAG 2." *Pietrzkowski* at col. 5, lines 60-65.

From this single statement, the Examiner concludes that "[i]t was routine to deliver antisense oligonucleotides to the lung." *Office Action* at page 6.

Appellants submit that the Examiner's statement is contrary to the evidence. The statement in Pietrzkowski is not accompanied by any examples (prophetic or working) of administering any oligonucleotide into the lungs. Rather, the only *in vivo* data in Pietrzkowski is an intra-tumor injection of antisense to IL-8. *See Pietrzkowski* at col. 5, lines 12-13. Nor do any of the other cited references disclose the administration of oligonucleotides into the lungs. An unsupported statement that one could administer oligonucleotides as an aerosol, without any evidence that anyone has actually ever done so, cannot support a conclusion that it was "routine" to do so. Appellants submit that the Examiner's assertion represents official notice without documentary evidence, as it is not common knowledge or well-known. Appellants request documentary evidence in support of the noticed fact, in accordance with M.P.E.P. § 2144.03.C. *See also In re Zurko*, 258 F.3d 1379, 59 USPQ2d 1693 (Fed. Cir. 2001); and *In re Ahlert*, 424 F.2d 1088, 165 USPQ 418 (CCPA 1970).

The cited references do not disclose antisense inhibition of gene expression in the lung

The second assertion which is not supported by the evidence is that the references provide a reasonable expectation that administration of ICAM-1 antisense into the lungs "would provide for inhibition of ICAM1 expression..." *Office Action* at page 5.

As explained above, none of the cited references disclose actuall y administering an oligonucleotide into the lungs. Given that there is no evidence that anyone has every administered an oligonucleotide compound into the lungs, the cited references cannot provide a reasonable expectation of successfully inhibiting gene expression by doing so.

Even if *arguendo* it would be obvious to do so, there is no evidence of record to support the conclusion that administration of ICAM-1 antisense into the lungs would reasonably be expected to inhibit ICAM-1 expression. To reach this conclusion, one must assume that administration of ICAM-1 oligonucleotides into the lungs is efficacious based on other successful routes of administration. However, there isn't a single example in the cited references of inhibiting any gene by administration of oligonucleotides into the lungs, and therefore no basis for such an assumption. Appellants submit that the Examiner's assertion represents official notice, and hereby request documentary evidence in support of the noticed fact, in accordance with M.P.E.P. § 2144.03.C. *See also In re Zurko*, 258 F.3d 1379, 59 USPQ2d 1693 (Fed. Cir. 2001); and *In re Ahlert*, 424 F.2d 1088, 165 USPQ 418 (CCPA 1970).

The cited references do not disclose inhibition of eosinophil recruitment into the lung

The third assertion which is not supported by the evidence is that the references provide a reasonable expectation that inhibition of ICAM-1 expression by administration of ICAM-1 antisense into the lungs "would provide for the treatment effects claimed..." – reduced eosinophil recruitment into the lungs. *Office Action* at page 6.

Appellants are not aware of any mention of ICAM-1 or eosinophils in Pietrzkowski or Wang. While the Bennett references disclose antisense to ICAM-1, Appellants are not aware of the mention of eosinophils anywhere in either of the Bennett references. This leaves only the Cook, Wright and Wolyniec references to support the Examiner's assertion.

The only disclosure regarding eosinophils and ICAM-1 in Cook is the following single sentence: "Moreover, intraperitoneal administration of a monoclonal antibody to ICAM-1 decreases ovalbumin-induced eosinophil infiltration into skin in mice." *Cook* at col. 30, line 33-36 (emphasis added, citation omitted). There are numerous differences between the claimed method and the disclosure in Cook: Cook relates to ICAM-1 antibodies, not oligonucleotide compounds; Cook relates to i.p. administration of the antibodies, not administration into the lung; and Cook relates to eosinophil infiltration into the skin, not the lung.

There is no evidence of record that one would expect the inhibition of eosinophil infiltration into the skin following i.p. administration of antibodies would be in any way predictive of eosinophil recruitment into the lung following oligonucleotide lung administration. Without this additional evidence, which the other cited references do not provide, the disclosure in Cook is not relevant to determining if the pending claims are obvious.

The Examiner asserts that Wright teaches "the administration of antisense in vivo to inhibit eosinophil infiltration and accumulation in the lungs (see esp. paragraphs 173-175, example 19)." *Office Action* at page 4. There is simply no support in Wright for this assertion.

Wright does not mention antisense in Example 19 or anywhere else (Appellants note that Wright does not contain paragraph numbers). Wright only mentions eosinophilia twice, in the paragraph spanning columns 19 and 20. Wright states:

> In vivo activity of these compounds [not antisense] can also be assessed in other models of inflammation predicted to involve elevated VCAM-1 levels. One such model for respiratory diseases, such as asthma, is an ovalbumin-sensitized model. This model of pulmonary inflammation is IgE mediated and involves eosinophillia (as does the asthmatic human). ... The effect of the claimed

> compounds, such as MDL 29,353, should be to suppress the upregulation of VCAM-1 expression and inhibit eosinophil accumulation in the BAL fluid. *Wright* at col. 19, line 57 through col. 20, line 5 (emphasis added, citation omitted).

This passage is purely speculative in nature – the activity "can be assessed" in models "predicted" to involve VCAM-1 and the effect of the compounds "should be" inhibition of eosinophilia. In addition, it is speculation regarding VCAM-1, not ICAM-1, the claimed compounds are small molecules, not oligonucleotides, and they are administered in food, not into the lung. *Id.* at col. 19, lines 40-43.

In addition, Appellants note that the small molecule inhibitors of Wright were tested *in vitro* and both VCAM-1 and ICAM-1 levels were examined. Not surprisingly, the tested compound's effect on VCAM-1 and ICAM-1 differed depending on the tissue, demonstrating that VCAM-1 and ICAM-1 are not interchangeable. *See Wright* at col. 19, lines 21-27.

Thus, contrary to the Examiner's assertion, Wright does not "teach the administration of antisense in vivo to inhibit eosinophil infiltration and accumulation in the lungs" – the reference doesn't disclose antisense, doesn't disclose its administration into the lungs, and contains only speculation about the role of VCAM-1 in eosinophils in the lung, not ICAM-1. Alone or in combination, Wright does not provide any basis for concluding that ICAM-1 oligonucleotides administered into the lung can reduce eosinophil recruitment into the lung.

The final reference relied on by the Examiner is Wolyniec. The Examiner asserts that Wolyniec teaches "reduced inflammation and eosinophilia in ICAM-1 deficient mice" and the essential role of ICAM-1 expression "in enabling eosinophils to enter the airways of an organism." *Office Action* at page 4. According to the reference, ICAM-1 knockout mice were tested in an animal model of asthma. However, the authors urge caution in drawing conclusions based on the experiments:

> [L]imitations in forming conclusions from gene-knockout mice should be considered. As an example, Kumasaka and colleagues have described a role for ICAM-1 in a model of endotoxin-induced lung neutrophilia. Antisense oligonucleotides and monoclonal antibodies to ICAM-1 provided inhibition of the lung neutrophilia, whereas the ICAM-1 gene knockout was comparable to the wild type. *Wolyniec* at page 778, left col., first full paragraph (emphasis added, citation omitted).

It is clear from this paragraph that antisense, antibody, and gene knockout experimental results for ICAM-1 are not necessarily predictive of each other.

In addition, Appellants note that knockout mice differ from mice administer antisense in an important way. Knockout mice are born ICAM-1 deficient, and never expressed ICAM-1. Thus their development of airway hyperresponsiveness following ovalbumin (OVA) was affected by the absence of ICAM-1 during the entire exposure period. In contrast, in the instant case administration of the ICAM-1 antisense began on day 15, after the animals were initially exposed to OVA on days 0 and 14. Thus, because knockout animals did not express ICAM-1 during the initial OVA exposure (sensitization stage) as well as during the challenge stage, knockouts are not equivalent to experiments in which antisense was administered only during the challenge stage. As patients with inflammatory diseases such as asthma presumably express ICAM-1 throughout their lives, the knockout experiments are less likely to reflect therapeutic efficacy than antisense experiments.

This assertion is supported by an additional example where the successful inhibition of a target *in vivo* by a non-oligonucleotide compound was not predictive of the *in vivo* activity of

oligonucleotide compounds to the same target, even where the oligonucleotide compounds worked *in vitro*. Appellants previously submitted evidence regarding the MAP kinase JNK, which is known to be involved in pulmonary inflammation and eosinophilia.

Wong (*Curr. Opin. Pharmacol.*, 2005, **5**:264-271; previously submitted) discloses that a non-oligonucleotide specific inhibitor of JNK reduces eosinophilia in the lung of rat and mouse models of pulmonary inflammation. *Wong* at page 269, col. 1 and Table 1. This is similar to the disclosure in the cited references relied on by the Examiner in the instant case – non-oligonucleotide compounds targeting ICAM-1 (e.g., antibodies and gene knock-outs) are apparently effective in reducing eosinophilia in skin and lung. Therefore, applying the Examiner's reasoning from instant case, because non-oligonucleotide inhibitors of JNK reduce eosinophilia *in vivo* as disclosed in Wong, antisense to JNK that are active *in vitro* would be expected to reduce eosinophilia *in vivo* as well. However, this conclusion is not supported by the evidence.

Appellants previously submitted a declaration by Brett P. Monia, an expert in the field with extensive knowledge of oligonucleotide compounds. The declaration discloses that two antisense molecules to JNK, selected on the basis of their *in vitro* inhibitory activity, were ineffective in preventing airway hyperresponsiveness or eosinophil recruitment into the lungs in a mouse model of airway hyperresponsiveness at three different doses. The mouse model used in the Monia studies is very similar to the model used in Examples 30-32 of the instant application, and the JNK antisense were administered into the lung as presently recited in the instant claims. Thus, in spite of the successful inhibition of eosinophilia using a non-oligonucleotide inhibitor of JNK as disclosed in Wong, antisense to JNK that were active *in vitro* were not effective at preventing eosinophil recruitment when administered via the lung.

These results further support the cautionary note made in the Wolyniec reference – antisense, antibody, gene knockout and small molecule inhibitor studies are not interchangeable. The knowledge that a particular target may be involved in eosinophilia, and that inhibiting the target using non-oligonucleotide means reduces eosinophilia, is not sufficient to conclude that oligonucleotide compounds to the same target administered via the lung will have the same effect. Given this evidence, Appellants submit that one of skill in the art would not have a reasonable expectation of success at practicing the claimed methods based on the cited references.

The Examiner's response to Appellants' arguments are not persuasive

In response to Appellants' arguments, the Examiner argues that "ICAM-1 was a known target in inflammatory disorders such as asthma, as evidenced by Bennett et al. (WO). It was routine to deliver antisense oligonucleotides to the lung." *Office Action* at 6.

As mentioned above, the evidence does not support the assertion that it was "routine" to deliver antisense to the lung. As for the assertion that ICAM-1 was a known target, this is not sufficient to provide a reasonable expectation of success for the particular method claimed in the instant application.

In response to Appellants' assertion that Wright does not provide any support for the Examiner's rejection, the Examiner states that "Wright et al. teach that inhibition of VCAM-1 would be expected to inhibit eosinophil accumulation in the BAL fluid," and combined with the teachings of Bennett WO, "one would reasonably expect for inhibition of VCAM-1 or ICAM-1, both taught to be asthma targets by Bennett et al. (WO) to have effects on eosinophil accumulation as taught by Wright et al." *Id.* at 7 (emphasis added).

As explained above, the disclosure in Wright is pure speculation involving non-antisense compounds targeting VCAM-1 administered in food. In addition, Wright demonstrates that VCAM-1 and ICAM-1 are not interchangeable. Even if Bennett WO teaches that VCAM-1 and ICAM-1 are both prospective targets for asthma treatment, one cannot reasonably combine the speculation in Wright regarding VCAM-1 with Bennett WO to reach the conclusion that ICAM-1 inhibition would affect eosinophilia. Combining speculation with further speculation does not provide a basis for an obviousness rejection in a field as unpredictable as biology.

Finally, the Examiner states that even if the teachings of Wolyniec are not identical to the instant specification because knock-out mice were used, this does not negate its teachings regarding ICAM-1's "essential role in enabling eosinophils to enter the airways of an organism, thereby offering an expectation that delivery to the lung of the specific oligonucleotide of Bennett et al. would in fact reduce eosinophilia." *Office Action* at page 8.

This conclusion assumes that ICAM-1 antisense can be administered into the lungs and that doing so successfully reduces ICAM-1 expression – assumptions for which there is no supporting evidence as discussed above. In addition, it ignores the teachings of Wolyniec – "limitations in forming conclusions from gene-knockout mice should be considered." The fact that knockout mice fail to develop eosinophilia does not mean that reducing ICAM-1 expression using oligonucleotides administered into the lung will reduce eosinophil recruitment into the lung.

Finally, the Examiner states that "[t]he question is not if the instant compound would inhibit ICAM-1 expression" because "[t]he instant oligonucleotide is known in the art and is known to be targeted to ICAM-1, which is a known asthma target." *Office Action* at 8. Appellants respectfully submit that this is exactly what the question is. None of the references disclose administration of an antisense compound into the lung, and none of the references show inhibition of any gene by this route of delivery. In addition, the only evidence that ICAM-1 expression influences recruitment of eosinophil into the lung is Wolyniec, which used knockout mice to prevent the development of airway hyperresponsiveness – they did not examine the role of ICAM-1 in eosinophil recruitment into the lung after airway hyperresponsiveness had developed.

In view of the above, Appellants respectfully submit that the Office has failed to establish a *prima facie* case of obviousness. Even if *arguendo* there was a reason to try to administer the compound of Bennett into the lung to reduce ICAM-1 expression, there must be a basis for one of skill in the art to have a reasonable expectation that doing so would reduce ICAM-1 expression sufficiently to reduce eosinophil recruitment into the lung. The speculation in the cited references is not sufficient, particularly in light of the unpredictability of the biological arts, as evidenced by the Monia Declaration. For at least this reason, Appellants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 103(a) as obvious over the cited references.

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